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Contribution:

Role of the Locus Coeruleus Arousal System in Cognitive Control

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Short title: LC-NE in Cognitive Control

Abstract

Cognitive control lies at the core of human adaptive behaviour. Humans vary substantially in their ability to execute cognitive control in order to optimally face environmental challenges, but the neural origins of this heterogeneity are currently not well understood. Recent theoretical frameworks implicate the locus coeruleus noradrenergic arousal system (LC-NE) in that process. Invasive neurophysiological work in rodents has shown that the LC-NE is an important homeostatic control centre of the body. LC-NE innervates the entire neo-cortex, and has particularly strong connections with the cingulate gyrus. Here, using a response conflict task, fMRI, and concurrent pupil dilation measures (a proxy for LC-NE firing), we provide empirical evidence for a decisive role of the LC-NE in cognitive control in humans: We show that the level of individual behavioural adjustment in cognitive control relates to the level of functional coupling between LC-NE and the dorso-medial prefrontal-cortex (DMPFC) as well as dorso-lateral prefrontal cortex (DLPFC). Moreover, we show that the pupil is substantially more dilated during conflict trials requiring behavioural adjustment than during no conflict trials. In addition, we explore a potential relationship between pupil dilation and neural activity during choice-conflict adjustments. Our data provide novel insight into arousal-related influences on cognitive control and suggest pupil dilation as a potential external marker for endogenous neural processes involved in optimizing behavioural control. Our results may also be clinically relevant for a variety of pathologies where cognitive control is compromised such as anxiety, depression, addiction and PTSD.

Introduction

Cognitive control is the ability to flexibly shape and constrain thoughts and actions in service of accomplishing internal goals [1]. A crucial aspect of cognitive control is the resolution of response conflict, which is essential for decision making and adaptive behaviour [2,3]. Response conflict arises when a pre-potent habitual response is suppressed for the choice of an alternative option that better fits present behavioral goals [1,4]. Humans vary substantially in the ability to resolve response conflict, but the neural origins of this heterogeneity are currently not well understood.

The prominent conflict-monitoring model of cognitive control assigns a central role to the dorso-medial prefrontal cortex (DMPFC). Classic work has shown that this region, spanning from anterior cingulate cortex (ACC) to the supplementary motor area (SMA), detects and monitors the level of behavioral conflict [5-8]. In this framework, DMPFC communicates this information to the dorso-lateral prefrontal cortex (DLPFC), which subsequently implements appropriate adjustments and resolves the conflict through cortical amplification of task-relevant information [1,9,10]. An early extension of this model speculated that noradrenergic arousal processes may play a crucial role in cognitive control and response conflict adjustments [11-13]. In addition, recent behavioral and pupillometry work suggested that variation in the functioning of the locus coeruleus-norepinephrine (LC-NE) arousal system may account for individual differences in cognitive control capacity [14,15]. However, to date very little *neurophysiological* evidence in humans associates the LC-NE arousal system with individual differences in conflict resolution. Just one previous fMRI study has so far suggested that different human brainstem nuclei may be activated during cognitive control [16].

In animals, tracing studies have provided evidence for anatomical [17-19] and functional connections between the conflict monitoring DMPFC and the LC-NE [20-23]. In addition, the

region mostly associated with conflict resolution, the DLPFC [24,25], is also well interconnected with regions in the DMPFC such as premotor cortex and via reciprocal connections with SMA and pre-SMA [26]. However, there is only limited knowledge as to how the functional coupling between DMPFC, DLPFC the LC-NE, and other connected regions relate to the individual capacity for behavioral adjustments.

An individual's capacity for conflict resolution is typically quantified via reaction time differences between conflict trials, which require the resolution of conflict and no conflict trials during which no such resolution is necessary [1,5,6]. The resolution of conflict is thought to incur processing costs due to the necessity to detect, monitor and finally adjust the behavioural conflict, which eventually results in longer reaction times for conflict as compared to no conflict trials. Importantly, the better an individual's capacity to resolve the behavioural conflict, the smaller these reaction time differences. In other words, better regulators of behavioural conflict exhibit smaller differences in reaction times between these two trial types. Here we use this reaction time difference score to quantifiy an individual's regulatory capacity and relate it to the functional coupling of DMPFC in order to provide neurophysiological evidence for the observed individual differences in behavior. In particular, we hypothesize that the locus coeruleus noradrenergic system (LC-NE) may play a crucial role in response conflict resolution and may underlie individual differences in capacity for cognitive control, as previously speculated [14]. For such a decisive role, the locus coeruleus arousal system is indeed in a unique functional position, as it innervates the entire neo-cortex with noradrenergic projections and has particularly strong connections with the conflict monitoring DMPFC [17,18,20]. Moreover its hypothalamic connections and responsivity to emotional and physiological stress indicate that it may play a critical role in regaining homeostasis and optimizing behaviour [27-29]. The LC-NE is also clinically relevant for a variety of pathologies in which cognitive control is compromised such as anxiety, depression, addiction and PTSD [30-37].

In addition to non-invasively measuring functional imaging data, we concurrently track variations in pupil size during congnitive control behaviour as LC-NE firing has been related to pupil dilation (Joshi et al. 2016). With this measure, we aim to establish a link between the cheap and easy acquired external pupil measures during response conflct resolution and neural activity in regions previously related to cognitive control [6,24,38].

Material and Methods

Participants. We recruited 48 medical students (n=28 women, mean age = 24 years, SD = 1.99) following standard exclusion criteria (fMRI safety, psychopathology). Participation was voluntary and participants provided written informed consent. After the study, participants were debriefed and compensated for their participation (CHF 35 per hour, which roughly corresponds to 35 US$). All procedures were approved by the Cantonal Ethics Committee of Zurich (KEK).

Stimulus presentation. All stimuli were displayed on a grey projection screen (using the Cogent2000-toolbox, http://www.vislab.ucl.ac.uk/cogent_2000.php, implemented in Matlab, The MathWorks, Inc., Natick, Massachusetts, United States) that participants viewed by means of a mirror system mounted atop the MR head coil. The task comprised 50 congruent and 50 incongruent trials, presented in pseudorandom order and counterbalanced for equal numbers of congruent-congruent, congruent-incongruent, incongruent-congruent, and incongruent-incongruent temporal stimulus pairings (however, please note that we only focus on simple congruency effects in this work and describe the trialwise sequence effects in another manuscript). Most participants conducted two runs of the emotional Stroop task (46 out of 48), which amounts to 200 trials. Two participants only did one run which amounts to 100 trials. The intertrial intervals (ITI) for each participant were individually sampled from a gamma distribution using the matlab function gamrnd.m (Matlab, Mathworks) with shape parameter 2

and scale parameter 1 and truncated within 2 and 6 seconds, to optimally spread 100 trials across 10 min of one functional run time. This yielded a mean ITI of 3.1 sec. To avoid any priming effects, there were neither direct repetitions of the same face with varying word distracters nor direct repetitions of exact face-word-distracter combinations [39,40]. Genders, identities, and affective expressions on the faces were randomized throughout the task and stimulus occurrences were counterbalanced across trial types and response buttons. Subjects were instructed to respond as fast as possible to the stimulus by pressing one of two buttons (left: happy, right: fear or vice-versa) on an MR-compatible response box, while trying to maintain high accuracy. In addition, each participant conducted 1-2 runs of an attentional capture task (10min per run, these data will be reported elsewhere).

Behavioral Task. We employed the emotional-Stroop task [38,41,42], a well-established laboratory measure of conflict [43,44]. Participants categorized faces according to their emotional expression (happy vs. fearful) while at the same time ignoring overlayed emotionally congruent (C) or incongruent (I) words ("HAPPY", "FEAR", **Figure 1A-B**). Behaviorally, the conflict is typically observed as higher reaction times (RT) for incongruent than congruent trials [38,41,45] (**Figure 1C**).

(Figure 1 about here)

Behavioral analyses. Behavioral data consisted of both reaction times (excluding error and post-error trials) and accuracy rates. A response was considered correct when the emotional valence of the face expression was correctly identified. Trials with response times above 2 standard deviations from the mean (across all trials) were excluded from analysis (and regarded as trials of no interest in the fMRI-models [38,41,46], see below). Statistical behavioral analyses were performed using paired t-tests implemented in the statistics toolbox in matlab comparing conflict (I) vs. no conflict trials (C). An individual score for response conflict resolution was

computed as the reaction time difference between congruent and inconguernt trials (**Figure 1C**).

fMRI image acquisition. Subjects performed two fMRI sessions of the emotional stroop task, each lasting 9.75 minutes. During each session, we acquired 225 T2*-weighted whole-brain echo planar images using a Philips Achieva 3 T whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with an 8-channel Philips sensitivity-encoded (SENSE) head coil. Imaging parameters were: 2600 ms repetition time (TR); 40 ms (TE); 37 slices (transversal, ascending acquisition); 2.6 mm slice thickness; 2.5 mm x 2.5 mm in-plane resolution; 0.65 mm gap; 90° flip angle. To measure at fully equilibrated magnetic field, five dummy-image excitations were performed and discarded before functional image acquisition started. Additionally, we acquired a high-resolution, T1-weighted 3D fast-field echo structural scan used for image registration during post-processing (sequence parameters: 181 sagittal slices; matrix size: 256 x 256; voxel size: 1 x 1 x 1 mm; TR/TE/TI: 8.3/2.26/181 ms).

fMRI image pre-processing. Image preprocessing and analysis were conducted using SPM8 (Wellcome Trust Centre for Neuroimaging). Functional images were slice-time corrected (to the middle slice acquisition time) and realigned (accounting for subjects' head motion). Each subjects' T1-weighted structural image was co-registered to the mean functional image and normalized to the standard T1-MNI template using the "Unified Segment" procedure provided by SPM8 [47]. The functional images were then normalized to the standard MNI template using the same transformation, spatially resampled to 2.5 mm isotropic voxels, and smoothed using a Gaussian kernel (FWHM, 6mm).

fMRI data-analysis. We estimated a general linear model (GLM) to identify regions associated with conflict processing, defined as the BOLD activation difference between I and C trials. This contrast was used to test whether any region covaried with the individual response conflict resolution score defined as the reaction time difference between congruent and inconguernt

trials (**Figure 1C**). The smaller the RT difference between these two trial types, the better the level of response conflict resolution of the participant. The GLM contained two indicator functions placed at the onset of each of the possible trial types (congruent and incongruent). An additional indicator function modelled the onsets for trials of no interest, which included: trials with reaction times 2 standard deviations above the participant's overall mean response time as well as error and post-error trials that may be associated with error-related cognitive processing [38,41]. The GLM regressed the blood-oxygen level-dependent (BOLD) signal in each voxel on these regressors and a set of hyperparameters modelling MR image auto-correlations with a first-order autoregressive model. Six motion parameters (obtained during the realignment procedure) were also included as regressors of no interest to account for participants' head motion. Furthermore, we included additional regressors that accounted for variance induced by eye-related variables (blinks and saccades, see below), to ensure that neural conflict responses are not confounded by these variables [48]. The model thus included additional indicator functions for the onsets of blinks and saccades.

First-level summary statistics were obtained by calculating the single-subject voxel-wise contrasts of incongruent>congruent trials (I>C, quantifying conflict) (**Figure 2**). Statistical inference was performed with a random-effects General Linear Model within the SPM8 framework. The whole-brain FWE-corrected statistical threshold was set to $P < 0.05$ with an initial cluster-defining voxel-level threshold of T = 3.275 (equivalent to uncorrected $P < 0.001$) [49,50]. For hypothesis-guided ROI analysis of the LC-NE arousal system and DLPFC, we applied small volume peak-level FWE-correction restricted to a 2SD-locus coeruleus volume mask [51] and a 10mm radius sphere centered around DLPFC coordinates reported by [16] for the I>C contrast (X,Y,Z=48,10,36).

Psychophysiological analysis (PPI). We added to our GLM design matrix the BOLD time-series extracted from a 5mm sphere centered on the DMPFC-peak (X/Y/Z: -7/13/55) identified

with the incongruent > congruent contrast. We also added two interaction terms corresponding to the interactions of the extracted BOLD time-course and the C and I regressors. Note that these interaction terms cannot be confounded by the main effects and interactions of all other experimental variables, which were accounted for by the regressors in the original design matrix. In a second-level analysis, the difference in functional coupling during conflict processing (I>C) was correlated across the whole brain with the response conflict resolution score (RT difference between I>C) (**Figure 3**).

Eye measures. During scanning, eye movements were sampled at 250Hz using an MR-compatible infrared EyeLink II CL v4.51 eye-tracker system (SR Research Ltd.). In order to account for the effects of eye movements and blinks on BOLD responses, we added them as regressors of no interest to the general linear model (see above). Saccades were defined as eye movements larger than 0.5 degrees visual angle [52]. Blinks were defined as periods of signal loss lasting longer than 80 ms and shorter than 2000 ms [53]; these epochs were removed from the pupil data and filled in by linear interpolation.

Pupil dilation. Pupil time-series were high-pass-filtered with a low cut-off of 0.05Hz followed by a low-pass-filter with a high cut-off of 4Hz. Each run-wise pupil time-series was z-scored. Trial-wise pupil data were extracted ±5 seconds from stimulus onset and averaged per subject according to conditions of interest (congruent, incongruent **Figure 4 A-B**). The contrast incongruent (I) > congruent (C) was computed for each participant. Time periods of significant difference from zero ($p<0.05$) across all participants were identified via one-sample-ttests versus zero (**Figure 4 B**) and corrected for multiple comparisons using a cluster-based permutation test (see below). For each participant, the I>C pupil dilation within the significant time intervals (grey shading **Figure 4B**) was averaged to derive one pupil dilation difference score per subject, reflecting the level of individual phasic noradrenergic tone [54-56] during response conflict resolution. This individual pupil score (I>C) was added as covariate in a 2nd

level analysis of individual BOLD contrasts (I>C). This analysis identifies brain regions in which the I>C difference is reflected in the I>C difference in pupil dilation and for which pupil dilation may thus be an external read-out (**Figure 4**).

Pupil dilation cluster-correction. To identify time windows during which the pupil dilation significantly differs between incongruent and congruent trials, while avoiding false positive clusters, we applied Bonferroni-correction [57,58] via a cluster-based permutation test following [49]. We used a cluster-forming threshold of T = 2.02 corresponding to a two-sided p-value of 0.05 given 47 degrees of freedom (N=48). The procedure first calculates the one-sample t-statistic across all participants' average difference between relevant contrasts for each 4-millisecond bins in the pupil dilation time series. Next, the size of continuous temporal clusters, defined as the number of adjacent time bins exceeding the cluster-forming threshold, were identified and tested against cluster sizes observed by chance. To this end, a null distribution of cluster sizes was generated by permuting the labels for each trial and time bin within-participant by flipping the sign of each time bin randomly 1000 times and recomputing the t-statistic across all time bins for each iteration. On each iteration the *largest* permuted temporal cluster was identified and stored in the null distribution. A cluster corrected p-value is computed by dividing the number of clusters in the null distribution exceeding the number of clusters in the data by the number of iterations.

Results

DLPFC relates to level of response conflict resolution

Our results replicate classic behavioral and neural effects of response conflict [6,24,38]. For instance, individuals are generally slower to respond to incongruent trials [45]. Comparing incongruent (conflict) with congruent (no conflict) trials, we found significantly increased RTs

(T_{47} = 9.88, p = 4.67 * 10^{-13}, **Figure 1C**) and decreased accuracy (T_{47} = -5.25, p = 3.65 * 10^{-6}, **Figure 1D**). Theoretical frameworks [5] and empirical findings [6,24,38] predict that the monitoring and processing of conflict is reflected in activity of the dorsomedial prefrontal (DMPFC) and anterior cingulate cortex (ACC). Thus, not surprisingly, the I>C contrast revealed the dorsomedial prefrontal cortex (DMPFC, $P_{(FWE)}$ = 0.032, X/Y/Z: -7/13/55) extending into anterior cingulate cortex, a region strongly associated with response conflict in several prior studies [6,24,38] (**Figure 2A**).

In order to identify the neurophysiological origin of the observed individual differences in behavior, we correlated each participant's reaction time difference score (I>C) with the corresponding differences in BOLD activity (**Figure 2B**) observed between conflict versus no conflict trials (I>C). As hypothesized, we found that the individual level of response conflict resolution was related to DLPFC activation strength ($T_{(FWE-SVC)}$ = 3.26, P = 0.041, X/Y/Z: 43/18/35). More specifically, the smaller the reaction time difference between conflict as compared to no conflict trials, the stronger the difference in BOLD activity between conflict versus no conflict trials in DLPFC. In other words, the stronger the DLPFC activity difference between conflict versus no conflict trials, the better the participants were able to adjust their behavior (**Figure 2B**).

(Figure 2 about here)

Relating DMPFC functional coupling to individual level of response conflict resolution

In order to establish a behaviorally-relevant link also between functional connectivity in the conflict monitoring region (DMPFC) and the rest of the brain, we again use the reaction time difference score (I>C) for each participant and correlated it with the differences in functional coupling of DMPFC during conflict versus no conflict trials (I>C) (**Figure 3A**). We found that the level of behavioral choice conflict adjustment is strongly reflected in the functional

coupling between DMPFC and DLPFC ($T_{(FWE)}$ = 5.14, P = 0.017, X/Y/Z: 43/31/35, **Figure 3B**) as well as between DMPFC and the bilateral locus coeruleus noradrenergic system (right LC: $T_{(FWE-SVC)}$ = 3.43, P = 0.005, X/Y/Z: 6/-37/-23, left LC: $T_{(FWE-SVC)}$ = 3.21, P = 0.009, X/Y/Z: -5/-37/-23, **Figure 3C**). Interestingly, we also found two additional clusters for which the connectivity difference between I>C was related to response conflict resolution performance: the fusiform face area (right FFA: $T_{(FWE)}$ = 4.77, P = 0.008, X/Y/Z: 53/-52/-18) as well as the intraparietal sulcus (right IPS: $T_{(FWE)}$ = 4.55, P = 0.046, X/Y/Z: 23/-65/38). These results indicate an enhancement of functional coupling between the conflict-monitoring DMPFC with regions representing task-relevant variables, in our case faces in the FFA. These findings substantiate the notion that neural representation of task-relevant variables are actively enhanced to help resolve behavioural conflict, which directly leads to enhanced performance, i.e., better behavioural adjustments.

(Figure 3 about here)

Exploring individual differences in neural activity during conflict processing to individual differences in pupil dilation

Given a previously established link between LC-NE firing and pupil dilation (but see Reimer et al. for a cholinergic account), we tested the hypothesis that differences in pupil dilation during the response conflict resolution process may also relate to neural activity in regions previously associated with cognitive control such as DMPFC or DLPFC or even with the locus coeruleus. We first investigated whether pupil dilation differs between conflict and no conflict trials. We found substantially enhanced pupil dilation in conflict versus no conflict trials within a time-window of 1 to ca 3.5 seconds post stimulus onset (**Figure 4A-B**), suggesting a potential noradrenergic contribution to choice conflict adjustment (continuous cluster between 945ms to 3668ms, $p<0.05$, one-sample t-test, corrected for multiple comparisons using cluster-based permutation test, two-sided, df = 47, please see methods for details). Additionally, we correlated the individual pupil dilation difference (I>C) during the identified significant time window with the BOLD activity difference (I>C). We did not find any region surviving our

stringent whole brain family-wise error correction criterion. However, for completeness we report here the biggest uncorrected cluster that related to pupil dilation differences (I>C), which was located in the anterior cingulate cortex (ACC: $T_{(uncorected)} = 3.25$, $P = 0.001$, X/Y/Z: 6/13/25, k= 53, **Figure 4C**).

(Figure 4 about here)

Discussion

A crucial aspect of human adaptive behaviour and decision-making is the resolution of response conflict. Humans vary substantially in the ability to resolve response conflict, but the neural origins of this heterogeneity are currently not well understood. Recent theoretical frameworks have proposed that noradrenergic arousal plays a role in this process, but little neurophysiological evidence links individual functioning of the human LC-NE arousal system to an individual's ability to resolve response conflict [14-16]. Here we provide such evidence. More specifically, we show that the level of individual conflict resolution (reaction time differences between conflict trials and no-conflict trials) is strongly related to the level of functional coupling between the conflict-monitoring region DMPFC and the LC-NE arousal system as well as the DLPFC. The more effective the conflict resolution, the stronger the functional coupling between these regions. Moreover, we show that pupil dilation is substantially enhanced during response conflict resolution as compared when no resolution is required. The presented data provide novel insights into the role of arousal systems for determining the individual ability to deal with response conflict and the capacity for cognitive control [1].

The classic conflict-monitoring theory of cognitive control posits that the anterior cingulate cortex (ACC) in the DMPFC serves the essential role of detecting and tracking behaviourally relevant levels of conflict that require resolution [1,6,24]. It has further been proposed that ACC

activity may serve as a signal that engages regulatory processes in the DLPFC to implement performance adjustments [10,59], suggesting that increased DLPFC activity during cognitive control performance may be related to beneficial behavioral control. Much to our surprise, very little data exists that link individual differences in conflict resolution performance to activity levels in the DLPFC or to the level of functional connectivity within these proposed cognitive control circuits [1]. Neverthless, our data support the classic model by revealing that participants with increased activity in the DLPFC during conflict resolution also exhibited enhanced response conflict adjustment performance. In addition, the relevance of the DLPFC in behavioural control performance is further corroborated by our functional connectivity data. We show that the stronger the functional connectivity between the monitoring region DMPFC and the regulation region DLPFC during behavioral conflict resolution, the better the cognitive control performance (i.e., the smaller the reaction time differences (I>C)). The same network was identified in a previous study investigating ACC/DMPFC functional connectivity during conflict processing with comparable picture-word interference stimuli as employed here [60]. Congruent with our results, the authors also found stronger functional connectivity between an ACC seed region and DLPFC in conflict vs. no conflict trials. Moreover, the importance of this network for behavioural control in general is supported by other studies of cognitive control with other modalities. For instance, using the stop-signal task, its been shown that the DMPFC shows greater activation during stop error as compared to go success trials, and that DLPFC shows greater activation during post-error go trials with RT slowing as compared to post-error go trials without RT slowing [61]. Moreover, electrophysiological evidence has also implicated this network in behavioral adjustment for proactive control [62].

The role of DLPFC in the conflict monitoring model is classically thought to engage in regulatory processes to implement performance adjustments depending on the level of conflict detected by the DMPFC [10,59]. It is further assumed that these regulatory processes particularly

impact on task-relevant regions [9] to enhance neural coding of task-relevant variables, thereby improving conflict resolution. In the emotional-stroop-task as employed here, participants are asked to focus on and report the emotion of a face while disregarding word distractors. In accordance with predictions from the conflict monitoring model, we find that during conflict trials, functional coupling between the face selective fusiform face area [63-65] and the DMPFC directly relates to the individual conflict adjustments performance. This result suggests that enhanced communication between monitoring and perceptual regions can substantially improve task performance and potentially also cognitive control as shown here. However, please note that our data cannot resolve whether the information regarding the level of conflict that requires resolution must first pass through the DLPFC [1,6,24].

Enhancing activity of regions coding task-relevant variables is a function also assigned to the locus coeruleus noradrenergic system (LC-NE) [66], but the role of LC-NE in tasks requiring active cognitive control has remained underexplored. Nevertheless, while resting-state fMRI studies have demonstrated LC-NE functional connectivity with brain regions involved in executive control [67,68], an active noradrenergic role in conflict processing and resolution has so far mainly been suggested [11], primarily based on recent behavioural and pupil dilation evidence using various types of paradigms involving cognitive control [14-16].

For instance, multiple studies have shown that across three cognitive control domains (updating, switching and inhibition), increases in task demands typically lead to increases in pupil dilation [69]. Specifically in Stroop interference tasks, multiple studies have previously reported increased pupil dilation in conflict (versus no conflict) trials, which are typically associated with increased effort required to resolve the conflict [69-73]. Please see van der Wel et al. 2018 for an excellent literature review on pupil dilation in cognitive control, clearly identifying pupillometry as a useful and robust neurophysiological research tool [69]. In addition, an increasing body of evidence has started to reveal the brain mechanisms that underlie effort-

related pupil dilation and has primarily shown correlations of noradrenergic locus coeruleus activity with pupil dilation [27,74,75], but also with ACC activity [74].

The notion that LC-NE activity enhances task performance on a multitude of perceptual tasks is longstanding and particularly grounded in rodent neurophysiology [76-81]. For instance, it has been shown that higher NE concentration in the rodent brain is associated with improvements in sensory encoding [76,82,83], better signal detection performance [78,84], and eventually increased sensory discrimination [85-87]. Moreover, heightened noradrenergic tone has been linked with faster and more accurate perceptual choices in humans and non-human primates [55,56,78,79,88]. Our findings now extend this performance-enhancing role of LC-NE activity to the behavioural domain of executive functions involving conflict resolution and cognitive control. We show that functional coupling between the conflict-monitoring region DMPFC and LC-NE during conflict adjustments is directly related to behavioural performance. These findings may suggest that depending on the level of conflict detected by DMPFC, the LC-NE arousal system may also help upregulate activity in regions coding task-releavant variables, similarly to the prescribed role for DLPFC. This interpretation accords with a previous finding that functional connectivity between LC-NE seed region and both DLPFC as well as ACC was enhanced during conflict trials as compared to no conflict trials [16].

These previous human LC-NE connectivity reports, as well as animal neurophysiological tracer studies, also directly link with our pupil dilation results, as these studies have indicated a prominent anatomical and functional connectivity between LC-NE and DMPFC and particularly the ACC [17,18,20]. Here we find much larger pupil dilations during conflict trials as compared to no conflict trials. Given the proposed link between LC-NE firing and pupil dilation, these findings suggest a noradrenergic contribution to response conflict resolution, as previously suggested [11,69,89-91], thereby corroborating theoretical considerations [11-15]. In addition, even though not surviving stringent cluster correction, the location of the ACC region

relating to pupil dilation differences (I>C) in our results corresponds to a region that has previously been associated with unsigned reward prediction error [92,93]. This is in line with the notion that pupil signals may reflect uncertainty and a behavioural surprise component that is highly salient and arousing [94,95].

Our study is not without limitations. Due to its small size and proximity to the ventricles functional imaging of the brainstem is difficult [96-98]. It is therefore not entirely clear whether our imaging results in the brainstem only reflect LC-NE activity or activity from neighbouring areas. Future studies may address this problem with more specialized imaging protocols. For instance, to enhance signal-to-noise ratio, high-field imaging at 7 Tesla in combination with partial brain coverage would allow particularly small (submillimeter) voxel resolution and reduce partial voluming effects in small structures of the brain and be less susceptible to pulsating artefacts from the adjacent 4th ventrical. Moreover, a T1-TSE sequence would allow direct and individual identification of the LC-NE via neuromelanin-sensitive contrast [51,99,100]. Neuromelanin-sensitive sequences are also clinically relevant and may provide substantial translational value. Previous studies using these imaging techniques have highlighted potential pathology of the LC circuit in neuropsychiatric conditions associated with deficits in cognitive control, such as for example in Alzheimer's and Parkinson's disease [101]. In addition, altered LC integrity in pathological aging has also been identified using these innovative sequences [102]. Irrespective of such considerations, the convergence of our imaging and pupil results provides important neurophysiological evidence that characteristics of an individual's LC-NE system may be one of the subcortical neuro-modulatory systems contributing to the capacity for cognitive control.

In conclusion, our data provide insights into the role of arousal systems for determining the individual ability to deal with response conflict. Moreover, our results establish pupil dilation as a valuable external marker for endogenous neural processes involved in adjusting and

optimizing behaviour. These findings may be clinically relevant for a variety of pathologies with impairments of cognitive control, such as anxiety, depression, addiction and PTSD.

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Author Contributions

M.G., B.K., and C.C.R. conceived of the project. M.G., C.C.R. and B.K. designed the study. M.G. collected the data. M.G. performed all analyses. M.G., C.C.R. and B.K. wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Competing Interests statement

The authors declare no competing interests.

Data Availability

The raw behavioral data will be made available on the data sharing repository: https://osf.io/

Code Availability

The experimental code will be made available at: https://github.com/mgrues/

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Figure Legends:

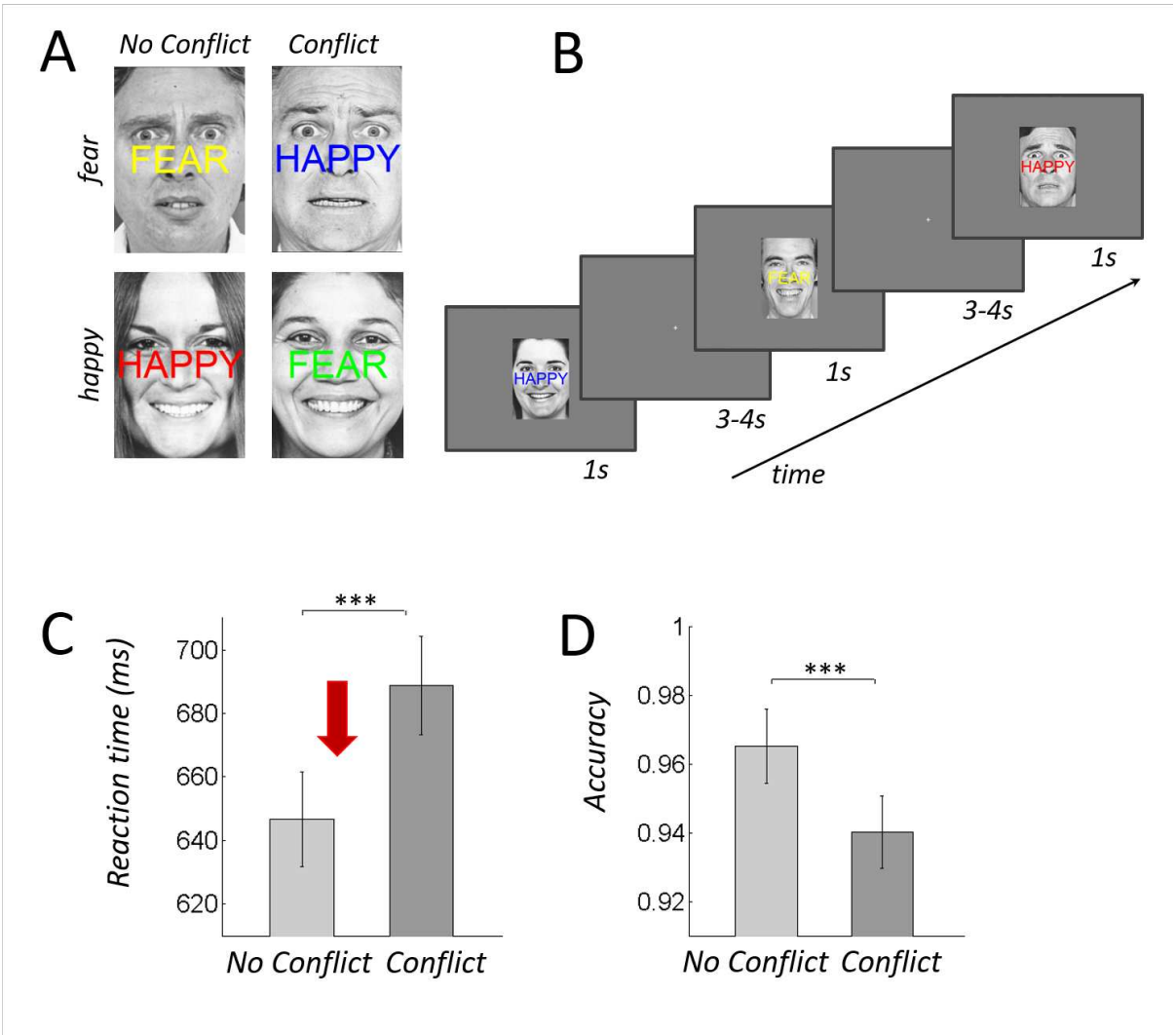

Figure 1. Experimental task and behavioral results.

(A): Example stimuli illustrating all four possible face/word combinations in the emotional-stroop task. Participants were instructed to react to the facial expression while ignoring the overlaid word and to answer as fast and accurately as possible. On each trial, the word color was randomly assigned in order to avoid adaptation effects. **(B)**: Example trial presentation schedule. **(C-D)** Conflict trials induce significantly more need for adjustment than co conflict trials, as indicated by **(C)** increased RTs and **(D)** decreased accuracy (N=48). Red arrow in C indicates the choice conflict adjustment score, which is defiened as difference between RTs in Conflict > No Conflict trials (I>C). The smaller the individual RT-difference (I>C), the better the participants capacity for choice conflict adjustment and cognitive control.

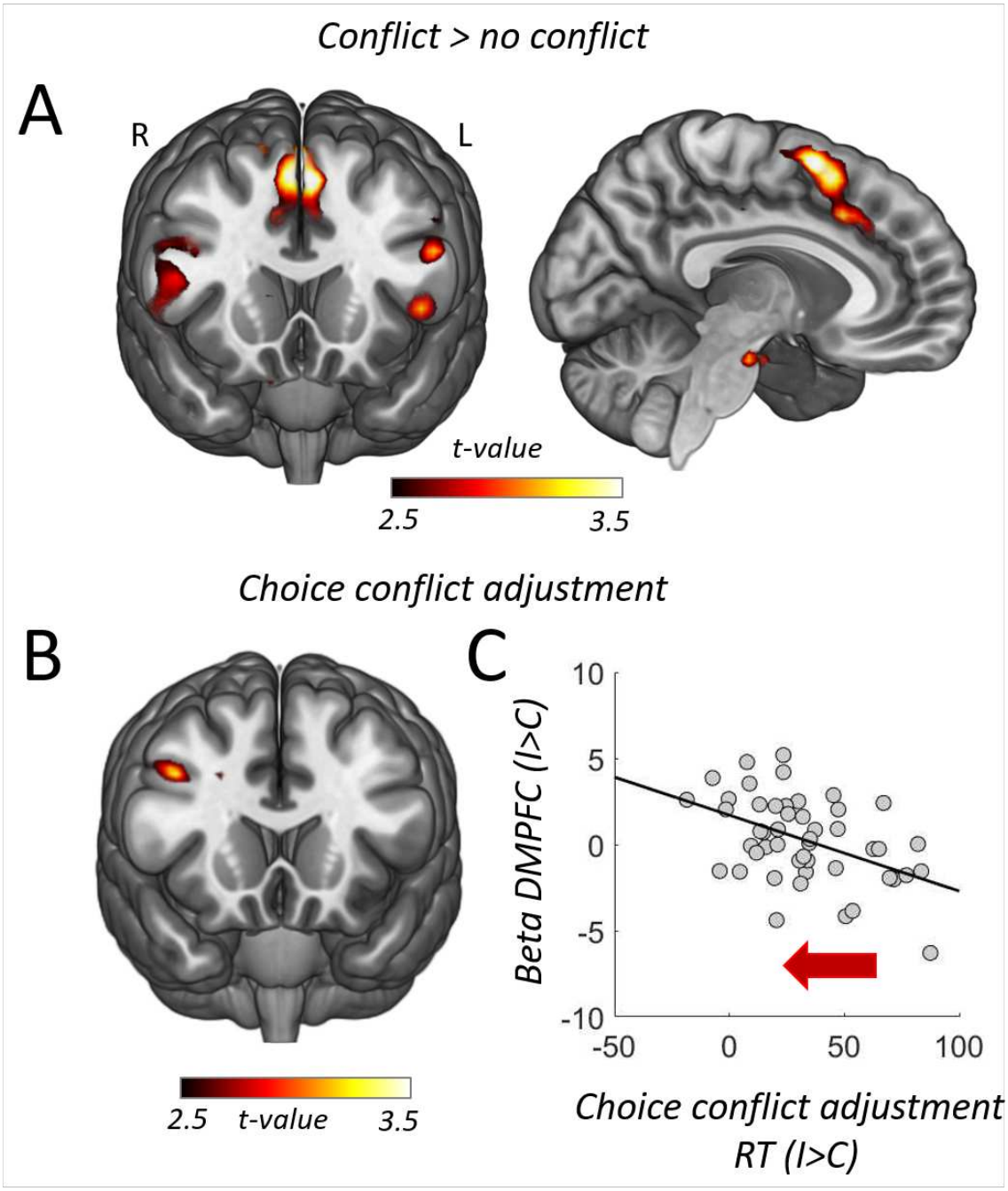

Figure 2. Conflict processing engages the DMPFC, while the level of response conflict resolution is reflected in DLPFC

(A) Response conflict (conflict trials > no conflict trials) activates the dorsomedial prefrontal cortex (DMPFC). **(B)** The smaller the RT difference between conflict and no conflict trials (the more effective cognitive control), the larger the activation in DLPFC for conflict > no conflict trials. **(C)** For visualization purposes we plot the correlation between the response conflict resolution score in RT and the BOLD signal differences (I>C) in the DLPFC coordinates at X/Y/Z: 43/18/35, (N=48). Neither of

these effects were observed in the LC-NE using small-volume correction (SVC). Red arrow indicates the response conflict resolution score, defined as the difference between RTs in Conflict > No Conflict trials (I>C). The smaller the individual RT-difference (I>C), the better the participant's capacity for response conflict resolution and cognitive control.

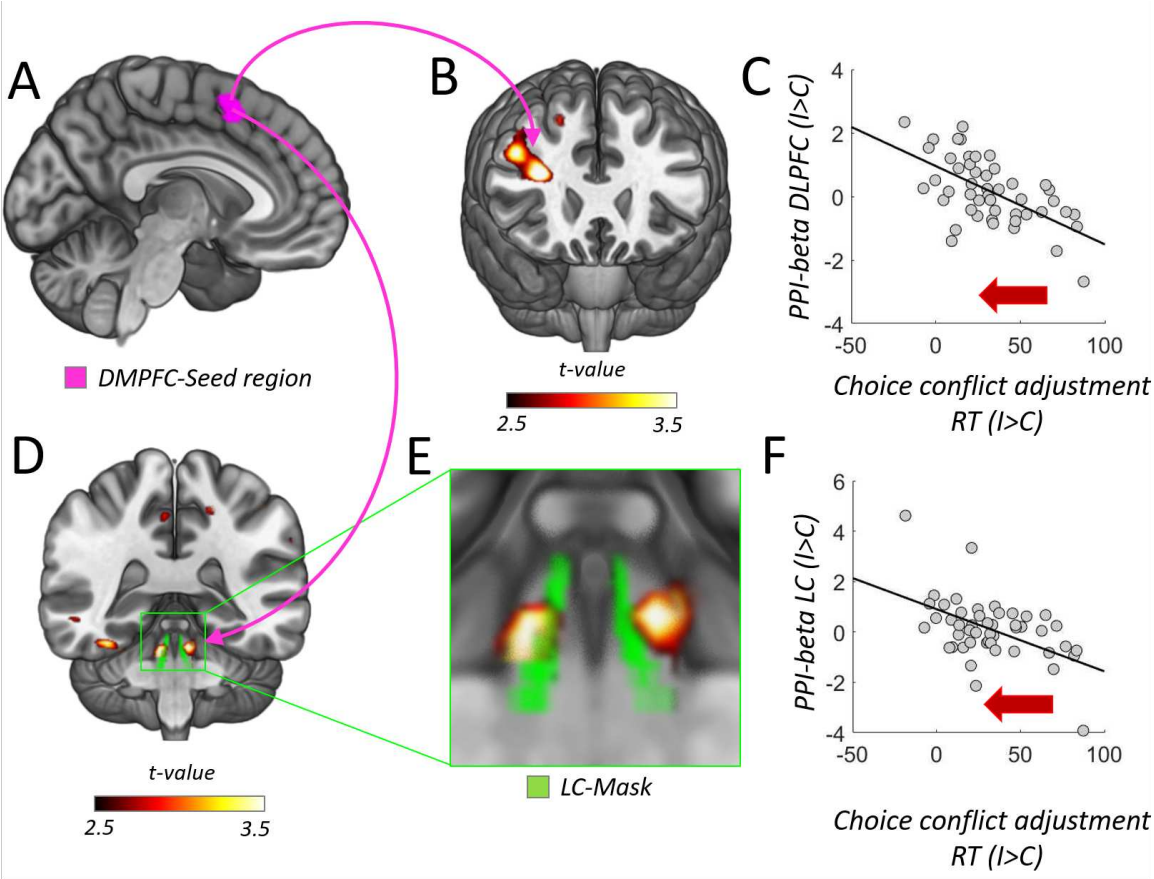

Figure 3. Individual levels of response conflict resolution relate to the strength of functional coupling between DMPFC and DLPFC and LC-NE

(A) DMPFC-seed region for whole brain functional connectivity analysis. **(B)** The smaller the RT difference between conflict and no conflict trials (i.e., the more effective cognitive control), the larger the functional coupling between DMPFC and DLPFC for conflict > no conflict trials. **(C)** For visualization purposes: the correlation between the response conflict resolution score in reaction time and the functional coupling between the DMPFC and peak voxel in the DLPFC (voxel coordinates at X/Y/Z: 43/31/35). **(D)** The smaller the RT difference between incongruent and congruent trials, the larger the functional coupling between DMPFC and LC for conflict > no conflict trials. LC-Mask

provided by Keren at al. 2009. **(E)** Enlarged view of the subcortical brainstem, indicating the LC-voxels in the 2SD-mask from Keren et al., 2009 (in green). **(F)** For visualization purposes: the correlation between the response conflict resolution score in reaction time and the functional coupling between the DMPFC and peak voxel in the locus coeruleus (voxel coordinates at X/Y/Z: 6/-37/-23, (N=48). Red arrow indicates the response conflict resolution score, defined as the difference between RTs in Conflict > No Conflict trials (I>C). The smaller the individual RT-difference (I>C), the better the participants capacity for response conflict resolution and cognitive control.

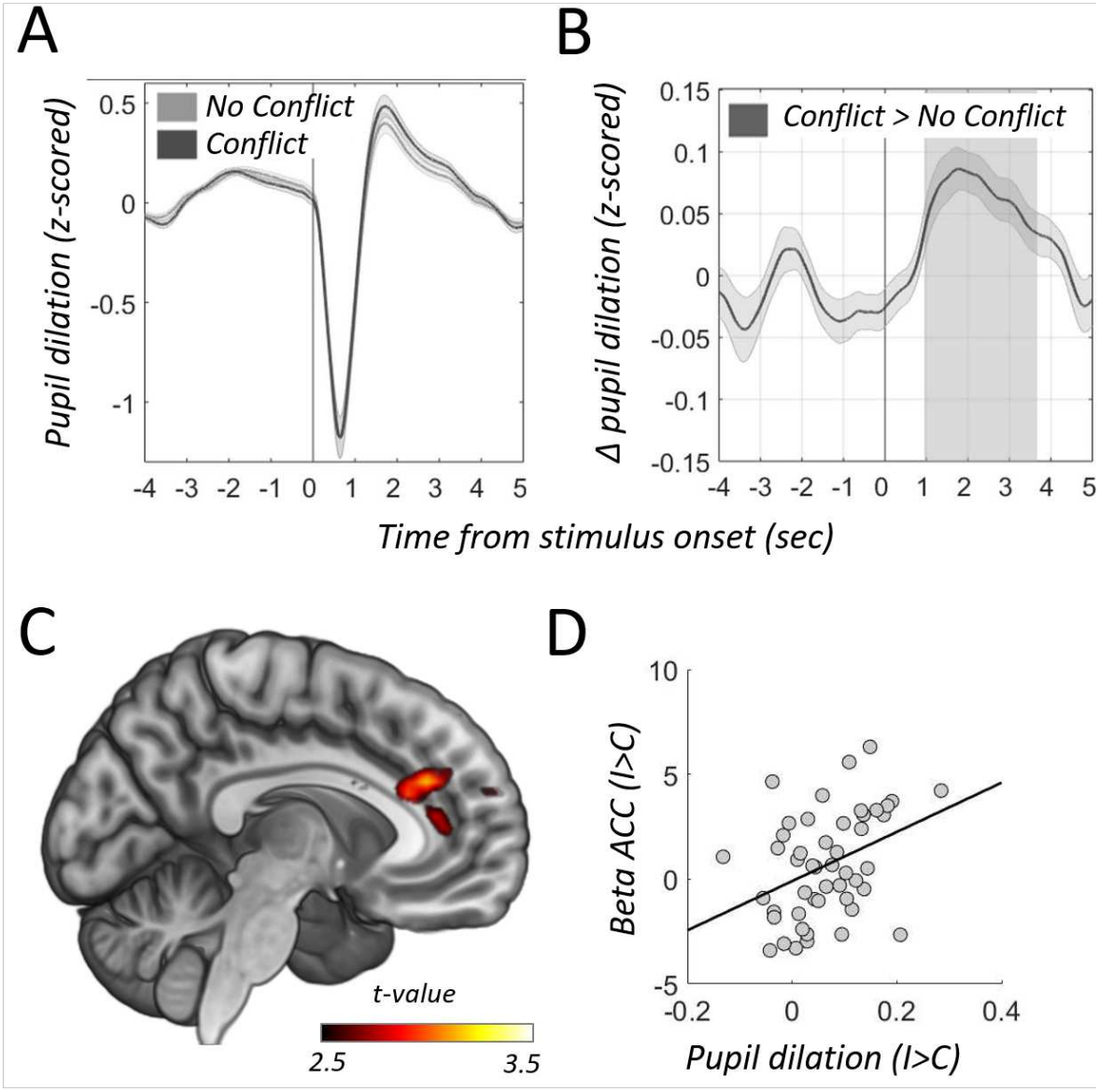

Figure 4. Pupil dilation during response conflict and its relationship to neural conflict signals.

(A) Mean Pupil dilation during conflict (dark grey) and no conflict trials (light grey). **(B)** Pupil dilation during conflict trials is significantly larger than during no conflict trials. Grey shades area = sign. difference $p < 0.05$ (cluster corrected). Vertical line = stimulus onset. **(C)** Pupil-dilation difference between conflict and no conflict trials correlates positively with the BOLD-difference between conflict and no conflict trials in the MPFC/ACC ($p=0.001$, uncorrected). **(D)** For visualization purposes: the correlation between the pupil dilation difference between conflict and no conflict trials (I>C) and the BOLD activity difference (I>C) in the anterior cingulate cortex (ACC voxel coordinates at X/Y/Z: 6/13/25), (N=48).